

Original Article

Toxic epidermal necrolysis: A study of clinical profile and treatment outcome in children

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Received – 16 February 2017

Initial Review – 13 March 2017

Published Online – 13 April 2017

ABSTRACT

Objectives: The objective of this study is to study the clinical and laboratory profile, risk factors for the development of blood culture positive septicemia and treatment outcome of children admitted with toxic epidermal necrolysis (TEN). **Methods:** All children admitted with TEN from January 2012 to January 2017 were included in the study. Blood culture, organ functions, and serum electrolytes were sent at admission and repeated as clinically indicated. Children were managed with reverse isolation in workforce limited setting of a Government Medical College Hospital. Outcome measure analyzed were the duration of hospital stay, development of blood culture positive septicemia and death. Children were followed up for a variable period from 2-month to 1-year. **Results:** A total of 13 children were admitted with TEN in the 5-year study period, aged 7.9 ± 3.2 years. Mean area of skin involvement was $69 \pm 19.9\%$. Drugs were found to be the most common cause of TEN accounting for 12 cases (92%). Evidence of renal injury was seen in 6 cases (46%). Disorders of sodium balance were the most common electrolyte abnormality observed in 11 cases (85%). There was no statistically significant difference in duration of progression of skin lesions in children who received ≥ 2 g/kg of intravenous immunoglobulin (IVIG) and those who received < 2 g/kg of IVIG. The mortality rate was 7.6%. At follow-up, all patients had dyspigmentation and none had scarring. 6 children (46%) had ophthalmic complaints at follow-up. **Conclusion:** Non-steroidal anti-inflammatory drugs were found to be the most common cause of TEN in children. Furthermore, TEN was found to be a disease causing critical kidney disease in children. Multi-organ dysfunction, hyperglycemia, and need for invasive ventilation were found to be associated with increased risk of developing culture positive sepsis. Low-dose IVIG, parenteral steroids and skin care with normal saline washes and sterile liquid paraffin impregnated gauze are the effective and safe treatment options for children with TEN in resource-limited setting.

Key words: Children, Intravenous immunoglobulin, Toxic epidermal necrolysis, Treatment, Skincare, Sterile paraffin gauze

Toxic epidermal necrolysis (TEN) is a rare severe disease of the skin and mucous membranes. It is considered a potentially fatal medical emergency [1] with a mortality rate of 25-30% [2]. TEN was first described in 1956 by Lyell [3]. Drugs are the most common cause of TEN and antiepileptics, sulfonamide antibiotics, penicillins, allopurinol, and oxicam nonsteroidal anti-inflammatory drugs (NSAID's) are the drugs commonly implicated in the development of TEN [4]. The pathogenesis of TEN is not fully understood but is believed to be immune-mediated as recurrence of TEN on re-challenging an individual with the same drug has been reported [5,6]. The clinical hallmark of TEN is a marked skin detachment caused by extensive keratinocyte apoptosis associated with mucosal involvement [7].

The incidence in adults is estimated to be between 0.4 and 1.2 cases/1 million people per year [8-12]. The disease is rarer in children compared to the adults [13,14]. There are very few studies on TEN in children. Most of the publications only present low number of pediatric patients ranging from 3 to 20 [15-20].

Mortality rate as high as 60% has been reported in children [17]. Studies including at least 10 children with TEN have reported a mortality rate range of 7-36%. Regional differences in the drug prescription and the genetic background of patients (human leukocyte antigen [HLA], metabolizing enzymes), can have an impact on the incidence of TEN [21,22]. Optimal treatment of TEN is controversial. Treatment with intravenous immunoglobulin (IVIG), steroids, cyclophosphamide, cyclosporine, and plasmapheresis has been described with varying effect. To decrease the rate of infection and protect the unhealed areas of skin with topical antibiotics, porcine xenograft, human skin allograft, etc., has been used [16,18,23,24]. Infections are the most common cause of death in TEN accounting for 50% of all deaths in TEN [25]. Infection rate as high as 90% has been reported in children [20].

Being a rare life-threatening disease, there is limited data regarding clinical and laboratory profile, complications, risk factors for septicemia, and outcome in children with TEN. This study was undertaken to study the clinical and laboratory

profile, risk factors for the development of blood culture positive septicemia and treatment outcome of children with TEN being treated in a resource-limited setting.

METHODS

This prospective observational study was conducted at pediatric intensive care unit (PICU) in Government Medical College, Thiruvananthapuram. All children admitted to PICU with TEN from January 2012 to January 2017 were included in the study. Patients were defined as experiencing TEN if they had large confluent blisters with positive Nikolsky's sign and involvement of more than 30% of total body surface area (TBSA). All children were also seen by a dermatologist for confirmation of the diagnosis. Children with other exfoliative skin diseases and those with skin involvement <30% of TBSA were excluded from the study.

Complete blood counts, C-reactive protein (CRP), blood culture, serum urea, serum creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum albumin, and serum electrolytes were sent in all cases. All children were managed in PICU with reverse isolation. Children were given daily skin care by cleaning of wounds and irrigation of intact skin with normal saline and whole body covered with autoclaved liquid paraffin soaked gauze (Fig. 1). Blisters were not punctured, and active debridement was not done. Antibiotic ointments were not applied routinely. They were used only for visibly infected areas after taking swabs for culture. All clothes and bed sheets of the patient for daily use were autoclaved. Caretakers were educated regarding the importance of asepsis. All cases were seen by an ophthalmologist and reviewed every alternate day. Caretakers were taught to provide eye care with 2 hourly lubricant drops and ointment and daily swiping of fornices to prevent synechiae. They were treated with the standard unit protocol of IVIG, injection betamethasone, and other supportive measures.

Data were collected using prestructured pro forma. Risk factors studied for the development of culture positive septicemia included the area of skin involvement more than 80%, mechanical ventilation, multi-organ dysfunction, and hyperglycemia

(>180 mg/dl). All these risk factors were treated as dichotomous variables, and Chi-square test was used for analysis. We also looked into the total duration of hospital stay and outcome at discharge and follow-up after 2 months. For continuous variables, mean and standard deviation was calculated, and the categorical variables were analyzed by Chi-square test.

RESULTS

Of 9967 PICU admissions, 13 patients were admitted with a clinical diagnosis of TEN including 7 males and 6 females with a mean age of 7.9 ± 3.2 years. There were no cases of TEN below 4 years of age. Mean area of skin involvement was $69 \pm 19.9\%$ of TBSA, and 7 cases (54%) had more than 80% skin involvement (Table 1). There was a history of drug ingestion before the onset of symptoms in 12 (92%) cases. In one case, there was no history of any drug ingestion. Anti-epileptic drugs (AEDs) were the causative agent in 5 cases (38%), while in 8 cases (62%), there was a history of ingestion of antipyretics (mefenamic acid in 5 cases and paracetamol in 3 cases). In 2 cases, there was co-ingestion of amoxicillin. All cases of TEN due to AEDs occurred after the 1st week of starting the AED (4 cases in 2nd week and 1 case in 4th week). In only 2 cases, there was a prior history of drug allergy (1 to amoxicillin and 1 to paracetamol).

A total of 11 cases (85%) had a fever at onset of skin rash that lasted for 2-7 days. 4 children (31%) had clinical and radiological evidence of the involvement of respiratory tract, out of which 3 had acute respiratory distress syndrome (ARDS). 7 (54%) children had involvement of gastrointestinal tract manifested as vomiting, abdominal distension, diarrhea, or feed intolerance (Fig. 2). All cases had ophthalmic involvement. Evidence of renal injury was seen in 6 cases (46%), out of which 5 had acute kidney injury (AKI) Stage II and I had AKI Stage III requiring renal replacement therapy.

Total blood count was normal (4000-11000 cells/mm³) in 9 cases (69%), while 2 cases (15%) had leukocytosis and 2 had leukopenia. In children with >80% skin involvement, 4 had normal counts, 2 had leukocytosis, and 1 leukopenia, while in children with skin involvement <80%, 1 had leukopenia and 5 had normal counts. There was no statistically significant association between total leukocyte count and severity of skin or systemic involvement. Respiratory involvement was seen in 4 cases at admission, out of which 2 had leukopenia, and 2 had normal counts. Three of the four cases with pulmonary involvement had evidence of severe ARDS and needed mechanical ventilation. Thrombocytopenia <10000 cells/mm³ was seen in only 1 case. CRP was elevated in 9 cases at admission; however, in 2 cases, CRP was not estimated at admission. Blood culture was sent at admission in all cases and was found to be sterile in all cases. 3 cases subsequently developed blood culture positive septicemia. Organisms isolated were hemolytic *Streptococci*, *Acinetobacter* species, and *Pseudomonas* in one case each. All three cases had more than 80% skin involvement, and two of them also had multiorgan dysfunction and ARDS.



Figure 1: (a) Extensive skin involvement in a child with toxic epidermal necrolysis, (b) skin being covered with paraffin impregnated gauze after irrigation with normal saline

Table 1: Clinical and laboratory profile of children with TEN

Age years/sex	TBSA involving %	Inciting drug	Duration of progression (days)	Duration of hospital stay (days)	TLC (cells/mm ³)	IVIG (g/kg)	AKI stage	Serum sodium mEq/L
5/female	85	Mefenamic acid	4	20	14000	2	II	127
5/female	78	Carbamazepine	4	13	13000	2	0	124
12/female	86	Homeopathic medicine	3	10	5600	1	0	132
5/male	88	Mefenamic acid	4	75	5200	1	II	150
5/male	92	Lamotrigine	6	24	5900	3	0	130
11/male	54	Mefenamic acid/phenytoin	5	12	5700	2	0	128
4/male	45	No drugs	5	10	7000	3	0	132
6/male	56	Mefenamic acid	5	11	3300	1	II	150
9/male	88	Mefenamic acid/amoxicillin	14	14	3500	1	III	154
6/female	46	Paracetamol/amoxicillin	4	10	4400	3	0	137
12/female	47	Paracetamol	3	13	7800	1	0	121
11/female	86	Carbamazepine	5	8	5100	2	II	129
12/male	46	Paracetamol	3	10	10,000	2	II	133

IVIG: Intravenous immunoglobulin, TEN: Toxic epidermal necrolysis, TBSA: Total body surface area, TLC: Total leucocyte count, AKI: Acute kidney Injury (0: No injury, Stage I: Increase in serum creatinine by 1.5-1.9 times baseline, Stage II: Increase in serum creatinine by 2-2.9 times, Stage III: Serum creatinine increase >3 times baseline)

Serum sodium level was abnormal in 11 cases (85%). Hyponatremia was the most common electrolyte abnormality observed it was seen in 8 cases (62%), while hypernatremia was seen in 3 (23%) cases. Abnormalities of serum sodium level was seen in all children with skin involvement >80% ($p<0.1$), 5 cases (71%) had hyponatremia and 2 (29%) had hypernatremia. In children with skin involvement <80%, 3 had hyponatremia (50%), and 1 had hypernatremia (33%). Hyperglycemia >180 mg/dl requiring insulin infusion occurred in only 3 cases (23%), out of which 2 had multi-organ dysfunction and Gram-negative septicemia, while in one case, skin swab from penile skin lesion grew *Acinetobacter* species while his blood culture was sterile. Hyperglycemia was found to be a risk factor for the development of culture positive septicemia ($p<0.01$). Hypoalbuminemia was seen in 10 cases (77%). Serum AST >40 IU/L was seen in 6 cases while AST >100 IU/L at admission was seen in only 2 cases, and both had skin involvement >80% and ARDS. In both these cases, AST subsequently increased to 795 and 2030 IU/L, respectively. In both these cases, ALT was also >50 IU/L. In all other children, ALT was normal at admission. High AST values above 100 IU/L was associated with severe systemic involvement in TEN ($p<0.001$).

Progression of skin lesions stopped within 5 days in 11 (85%) cases. In one case, new necrotizing lesions continued to appear till the child succumbed to multiorgan dysfunction on day 14 (Fig. 3). 6 children received 2 g/kg IVIG, while 3 received 3 g/kg and 4 received 1 g/kg IVIG due to cost constraints. There was no statistically significant difference in the duration of progression of skin lesions between those who received >2 g/kg IVIG and those who received <2 g/kg of IVIG. All children received parenteral steroids also as injection betamethasone in a dose of 0.1-0.2 mg/kg/dose 8 hourly.

The median duration of hospital stay was 18 days (range 8-75 days). There was only one death with mortality rate of 7.6%, and this child succumbed on day 14 after admission. This child

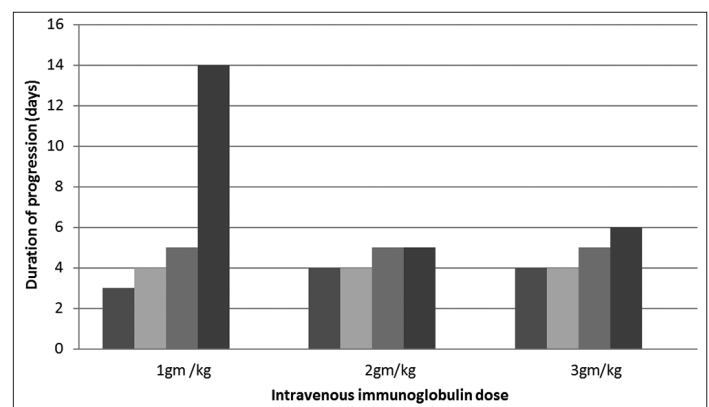


Figure 2: Intravenous immunoglobulin dose and duration of progression of skin lesions

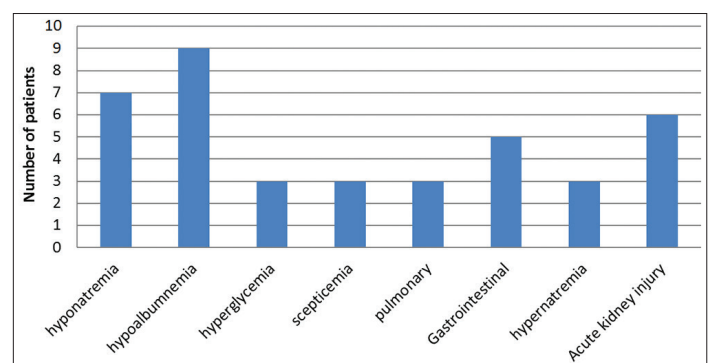


Figure 3: Complications in children with toxic epidermal necrolysis

had multi-organ dysfunction, oliguric renal failure requiring dialysis for renal support, liver failure, and catecholamine-refractory shock, ARDS requiring ventilator support on the day of admission, *Pseudomonas* septicemia and disseminated intravascular coagulation. The inciting drug was mefenamic acid. The children were followed up for a variable period from 2 months to 1 year. One child was lost to follow-up. All other children had skin dyspigmentation at follow-up and none had

scarring. 6 (46%) of children had ophthalmic complaints at follow-up such as itching, conjunctival xerosis, nasolacrimal duct obstruction, and chronic conjunctivitis.

DISCUSSION

TEN is a rare mucocutaneous disease accounting for 0.12% of total PICU admission in our study, and a total of 13 patients were during the 5-year study period. The mean area of skin involvement was $69.3 \pm 19.9\%$, and drugs were found to be the most common cause of TEN, accounting for 12 (92%) cases. Other studies have also implicated drugs as the causative agent in TEN in 77-100% cases [8-11,24]. NSAID's were the most common accounting for 8 (62%) cases, while antibiotics were implicated in only 2 cases (15%). In a survey of TEN in children by Levi et al. [26], a possibly increased susceptibility to acetaminophen in children compared to adults was observed. In a study by Spies et al. [24], antibiotics were implicated in 73% of the cases. A study from West Germany [11] has also reported antibiotics as the most common causative drug. In our study, antibiotics were implicated in only 2 cases (15%), which is in accordance with studies from India by Mangla et al. [27] and Das et al. [28] where antibiotics were implicated in only 20% of the cases.

TEN due to AEDs occurred within 4 weeks of introduction of the drug as has been described before by Roujeau et al. [29]. In all cases where NSAID's or antibiotics were implicated, the symptoms started within 48 h of ingestion of the drug while in cases of AEDs, it was reported after 1 week of starting the drug. In the study by Spies et al. [24], the mean duration of medication until the first symptoms of TEN occurred was 11 ± 2 days. Regional differences in drug prescription and genetic background of patients (HLA, metabolizing enzymes, etc.) may be responsible for the difference in the clinical presentation. A unique and strong association between HLA, drug hypersensitivity, and ethnic background has been discovered by Chung et al. [30].

Fever at the onset of symptoms was present in 10 cases (83%) as has been described in other studies. The absence of blood stream infection (documented by a negative blood culture in 92% cases at admission) despite having a fever in 11 (85%) and positive CRP in 9 (69%) cases at admission highlight the fact that sepsis develops during the disease and not at the onset. Hence, prophylactic antibiotics at admission in these children seem to be of doubtful value. Surveillance cultures from skin and blood, and starting antibiotics on the reappearance of fever or other systemic signs of infection appears to be a more rational approach. *Staphylococcal aureus* has been described as a common cause of early onset septicemia in patients with TEN [25,31], but in our study, there were no cases of *Staphylococcal* septicemia. There were two cases of Gram-negative septicemia (1 *Acinetobacter* species and 1 *Pseudomonas*) which has been reported in other studies also [30,32]. Infections and sepsis are the main causes of death in TEN patients [33,34]. Skin involvement $>80\%$ ($p < 0.1$), multi-organ dysfunction ($p < 0.01$), and need for invasive ventilation ($p < 0.01$) were found to be associated with increased risk of developing culture positive sepsis in our study. Leukopenia

has been described as a bad prognostic indicator [34], but in our study, total blood counts did not show any relation with extent of skin involvement, duration of hospital stay or development of multiorgan dysfunction.

Evidence of AKI was seen in 6 cases (46%) and a child with AKI Stage III developed anuric renal failure with multi-organ dysfunction, and renal support was provided with peritoneal dialysis. High serum urea is considered a bad prognostic indicator [34] but the staging of renal injury has not been done in other studies. The high incidence of renal injury and favorable outcome with conservative treatment points to the need of meticulous fluid therapy in these children and need for avoidance of nephrotoxic drugs in all children with TEN. Pulmonary involvement was seen in 4 cases (31%), of which three needed invasive ventilation within 24 h of admission for ARDS. Endotracheal aspirate sent soon after intubation was found to be sterile in all the three ventilated children. Early onset of respiratory symptoms and sterile endotracheal aspirate points to the fact that respiratory symptoms in TEN is often due to involvement of respiratory mucosa by the disease and not due to secondary infection. Gastrointestinal tract involvement in the form of vomiting, abdominal distension, diarrhea, or feed intolerance was seen in 6 (46%) cases. Similar pulmonary and gastrointestinal involvement has been reported in other studies [24].

Serum sodium level was abnormal in 11 cases (85%) at admission with hyponatremia in 8 and hypernatremia in 3 cases. In the study by Bastuji-Garin et al. [34], abnormal sodium level was seen in only 6% of the cases; however, this study mainly included adults with a mean age of 42.3 ± 19.8 years. The high incidence of sodium imbalance in our study may be because children with their larger body surface area compared to adults are more susceptible for water and electrolyte loss through their skin. Hyperglycemia at admission has been found to be a bad prognostic indicator [34]. In this study, no case had hyperglycemia at admission. Three children subsequently developed hyperglycemia with a blood glucose level >180 mg/dl and required insulin infusion. All the three cases had evidence of infection at the time of hyperglycemia. Hyperglycemia was found to be a marker of secondary bacterial infection ($p < 0.01$). Hypoalbuminemia was found in 77% of children with TEN. AST was elevated in 6 (46%) children. Bastuji-Garin et al. also reported AST level >40 IU/L in 59% of patients with TEN. In our study, AST >100 IU/L was observed in only 2 cases and both of these cases had skin involvement of $>80\%$ TBSA, multi-organ dysfunction, and ARDS. 1 child had a prolonged hospital stay of 75 days and needed invasive ventilation for 56 days while the other child also needed ventilatory support on the day of admission and succumbed to multiorgan dysfunction on day 14 after admission. High AST levels >100 IU/L at admission was found to be a marker of severe systemic involvement in TEN ($p < 0.001$).

In 85% of cases, the skin lesions stopped progressing by day 5 of onset of symptoms. We did not find a significant difference in duration of progression of skin lesions in children who received either <2 or >2 g/kg of IVIG. Many studies have

investigated the role of IVIG in TEN, but the results have been conflicting [35-37]. Studies showing both dose-dependent survival benefit with IVIG and studies showing no mortality benefit compared with supportive therapy alone or when compared with the mortality predicted by score for TEN have been reported in literature [36-38]. Mangla et al. [27], in 10 children with TEN, used low-dose IVIG (0.05-0.1 g/kg/day for 5 consecutive days) and reported a beneficial effect with no mortality. Tristani-Firouzi et al. [39] in a retrospective study in pediatric population using IVIG (0.5-0.75 g/kg/day \times 4 days) in 8 children also found it to be efficacious. A lower dose of IVIG (<2 g/kg) was found to be a safe and efficacious treatment for TEN in our study also. Progression of skin lesions beyond day 7 of onset of symptoms was associated with poor outcome ($p < 0.05$).

There was only one death with mortality rate of 7.6% which is less than the previously reported mortality rate of 25-30% [1]. Mortality rate, as high as 60%, has been reported in children with severe TEN [17]. Various topical skin care regimens have been advocated including skin grafting and topical antibiotics. Patients with extensive skin involvement are usually recommended to be treated at burn centers. In our case, all children were treated in the PICU with reverse isolation. Prendiville et al. [19] also reported successful treatment of 7 children with TEN in a pediatric hospital without any mortality. Topical antibiotic creams were not applied routinely in our study. They were used only at specific sites which looked infected. Daily skin care was provided by cleaning of wound and irrigation of unaffected skin with normal saline and whole body covered with autoclaved liquid paraffin impregnated gauze. This prevented adhesion of the skin to the dressing and paraffin in addition to preventing drying, and decreasing itching probably acted as a barrier for entry of organisms too. Our mortality of 7.6% is comparable to the 7% mortality rate reported by Spies et al. in their study on treatment of TEN with human allograft skin. Our study proves that very good treatment outcome can be achieved in patients with potentially life-threatening TEN even in resource-limited setting by appropriate skin care and health education of primary caretakers of the child.

As with most other studies on TEN small sample size is the limitation of our study. Being a rare, but severe life-threatening disease, more multicentric studies are needed to elucidate the clinical profile and identify the optimal treatment for TEN in children.

CONCLUSION

NSAID's were found to be the most common cause of TEN in children. Skin involvement more than 80%, multi-organ dysfunction, hyperglycemia and need for invasive ventilation were found to be associated with increased risk of developing culture positive sepsis in our study. IVIG with parenteral steroids and skin care with normal saline washes and sterile liquid paraffin impregnated gauze was found to be an effective and safe treatment options for children with TEN.

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Sugunan S, Kumar KKS, Sreenivasan P, Balachandran N. Toxic epidermal necrolysis: A study of clinical profile and treatment outcome in children. *Indian J Child Health*. 2017; 4(2):145-150.